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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/705,745 | 11/10/2003 | Torben Lauesgaard Nissen | 0208us520 | 4296 |

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| EXAMINER | |
|---|---|
| LUCAS, ZACHARIAH | |
| **ART UNIT** | **PAPER NUMBER** |
| 1648 | |

DATE MAILED: 03/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/705,745 | NISSEN ET AL. | |
| | Examiner | Art Unit | |
| | Zachariah Lucas | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *34-67* is/are pending in the application.

4a) Of the above claim(s) *37-39,45,46 and 55-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-36,40-44 and 47-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election of Group I, and the species wherein the G-CSF has the substitutions Q70K, K16R, K34R, and K40R, in the reply filed on January 5, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 37-39, 45, 46, and 55-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species or inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 5, 2005.

3. Currently, claims 34-36, 40-44, and 47-54 are pending and under consideration.

### *Information Disclosure Statement*

4. The information disclosure statement filed January 5, 2005, (stamped January 10, 2005) fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) **the application number of the application in which the information disclosure statement is being submitted on each page of the list;** (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The

information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

### *Specification*

5. The use of the trademark Neupogen® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that occurrences of the term "Neupogen®" be amended to include a generic statement such as - - Neupogen® hG-CSF- - or that the trade name be deleted and replaced by the generic descriptive - - unconjugated hG-CSF. - -

Appropriate correction is required.

### *Claim Rejections - 35 USC § 103*

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 34-36, 40-44, and 47-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishikawa et al. (U.S. Patent 6,166,183), in view of the teachings of Shaw et al.

(U.S. Patent 4,904,584), and of the teachings of Cox et al. (WO 99/03887) and Zurfluh et al. (6,100,070). The rejected claims read on G-CSF variants, or conjugates or compositions thereof, wherein the lysines at positions 16, 34, and 40 (relative to SEQ ID NO: 1) are replaced with arginines, and the Glutamine at position 70 is replaced with a lysine.

Ishikawa teaches the conjugation of G-CSF with a polyethylene glycol (PEG) to improve the in vivo bioactivity of the protein. Columns 1-2. The reference further teaches that the PEG may be conjugated to the protein through a lysine residue. Cols. 2-3. However, the reference does not teach the addition of a lysine residue to the protein for this purpose, teach or suggest the specific substitutions to SEQ ID NO: 1.

Shaw also teaches the modification of proteins by replacing naturally occurring lysine residues with non-lysines, preferably arginine, and substituting a lysine for a non-lysine residue. Abstract, col. 3, lines 36-43. The reference teaches that such modification is performed so as to control the attachment site of a molecule, such as PEG, to the protein. Col. 1. The reference teaches both the substitution of lysines within the native sequence for other residues, including arginine, and the addition (through substitution) of new lysines into the sequence for attachment of PEG. Column 3, lines 36-52. Further, the reference specifically teaches, as useful G-CSF mutants, variants wherein the lysines at positions 16, 34, and 40 have been substituted for arginine. Columns 13-14. See also, Osslund et al. (U.S. 5,581,476- columns 29-30, Figure 5, demonstrating that mutants of residues 16 and 40 have G-CSF activity); and Zurfluh et al. (U.S. 6,100,070 (teaching at column 93 that a substitution of residue 34 would also maintain G-CSF activity). The reference therefore renders obvious the use of a G-CSF with the indicated substitutions at lysines 16, 34, and 40. The combination of Shaw with Ishikawa teaches the

modification of G-CSF by substituting the lysine residues with arginine, and substituting another residue with lysine for PEG attachment. However, these two references do not teach or suggest the substitution of Q70 with a lysine, or the conjugation of a PEG molecule thereto.

The Zurfluh patent also teaches useful variants of G-CSF. While this reference is primarily concerned with other modifications than those of Shaw and Ishikawa, the reference also identifies operable analogues of G-CSF. Columns 92-94. Because these analogues are disclosed as having G-CSF activity, it would have been obvious to those in the art to modify as suggested by Shaw and Ishikawa as functional equivalents of the G-CSF of SEQ ID NO: 1. Among these equivalent analogues is a protein comprising a mutation at position 70. Thus, the reference teaches that mutations may be made for the glutamine at position 70. In addition to these teachings, the Cox reference also suggests modification of this residue. Further, this reference is teaching the substitution of this residue for a cysteine such that a cysteine reactive moiety, such a PEG, can be attached to the substituted residue. See, Cox, abstract, and page 43. Thus, the reference is teaching the modification of glutamine 70 for the same purpose as the Shaw and Ishikawa references. In view of the teachings of Zurfluh, indicating that substitution of this residue does not nullify G-CSF activity, and the teachings of Cox suggesting this residue as a potential PEG-attachment site, it would have been obvious to combine these teachings with those of Shaw and Ishikawa, and to substitute the residue with a lysine rather than a cysteine (a functionally equivalent modification). The combined teachings of these references therefore render the claimed compositions obvious.

***Double Patenting***

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 34-36, 40-44, and 47-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 5, 7, 11, 12, 14-17, and 19 of U.S. Patent No. 6,831,158. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the patent comprise overlapping subject matter with the claims presently under consideration. See e.g., claim 7 (claiming a polypeptide conjugate falling within the scope of the present claims). Because the present claims appear to be generic to, and define an obvious variation over, the claims of the patent, the present claims are rejected for obviousness type double patenting.

10. Claims 34-36, 40-44, and 47-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, and 14-21 of U.S. Patent No. 6,646,110. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the patent comprise overlapping subject matter with the claims presently under consideration. See e.g., claim 7 (claiming a polypeptide conjugate falling within the scope of the present claims). Because the present claims appear to be

generic to, and define an obvious variation over, the claims of the patent, the present claims are rejected for obviousness type double patenting.

11. Claims 34-36, 40-44, and 47-54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 7-15, 17, 19, 20, and 22 of U.S. Patent No. 6,555,660. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the patent comprise overlapping subject matter with the claims presently under consideration. See e.g., claim 22 (claiming a polypeptide conjugate falling within the scope of the present claims). Because the present claims appear to be generic to, and define an obvious variation over, the claims of the patent, the present claims are rejected for obviousness type double patenting.

12. Claims 34-36, 40-44, and 47-57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 26, 27, 29, and 33-40 of copending Application No. 10/318,966. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application comprise overlapping subject matter with the claims presently under consideration. See e.g., claim 26-28 (rendering obvious a polypeptide conjugate falling within the scope of the present claims). Because the present claims appear to be generic to or fall within the scope of, and define an obvious variation of, the claims of the copending application, the present claims are rejected for obviousness type double patenting. While it is noted that the claims of the copending application do not teach each of the limitations of the present claims, such additional

limitations are described in the specification of the application providing descriptive support for the polypeptides claimed by that application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 34-36, 40-44, and 47-57 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 5-10, 12-16, and 19 of copending Application No. 11/004461. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application comprise overlapping subject matter with the claims presently under consideration. Because the present claims appear to be generic to or fall within the scope of, and define an obvious variation of, the claims of the copending application, the present claims are rejected for obviousness type double patenting.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. The above rejection is, in part, based on the specification of a previously issued patent, rather than the claims. In support of the use of this material, the examiner notes the following excerpt from MPEP section 804 II(B)(1):

> When considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art. This does not mean that one is precluded from all use of the patent disclosure.
>
> The specification can always be used as a dictionary to learn the meaning of a term in the patent claim. In re Boylan, 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). Further, those portions of the specification which provide support for the patent claims may also be examined and considered when

> addressing the issue of whether a claim in the application defines an obvious variation of an invention claimed in the patent. In re Vogel, 422 F.2d 438, 441-42, 164 USPQ 619, 622 (CCPA 1970). The court in Vogel recognized "that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim," but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first "determine how much of the patent disclosure pertains to the invention claimed in the patent" because only "[t]his portion of the specification supports the patent claims and may be considered." The court pointed out that "this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, since only the disclosure of the invention claimed in the patent may be examined."

Thus, the courts have held that it is permissible to use the specification in determining what is included in, and obvious from, the invention defined by the claim on which the rejection is based. This is true even where elements are drawn from the specification describing the claimed invention which are not elements in the claim itself.

***Conclusion***

15. No claims are allowed.

16. The following prior art references are made of record and are considered pertinent to applicant's disclosure. However, while relevant they are also not used as a basis for rejection for the stated reasons.

> U.S. Patent Number 5,581,476, issued to Osslund (cited above), describes a G-CSF conjugate comprising Arginine substitutions for residues K16, K34, and K40. See, SEQ ID NO: 72 (the numbers are one off because the numbering begins at the starting residue Met, rather than at Thr where the numbering begins in the claimed sequence), and Tables 2 (cols. 21-24), 4 (cols. 27-28), and 5 (cols. 29-30). Finally, the reference also teaches that polymers may be conjugated with the G-CSF through additional lysines added to the protein. Col. 8, lines 43-49. However, the reference does not teach the advantage of making substitutions for these three lysines, and therefore cannot render obvious the combination of the substitutions with the other substitutions of the claimed inventions.
>
> Yamasaki et al., Drugs Exptl. Clin. Res. 24(4): 191-196. This reference teaches that G-CSF/polymer conjugates with reduced in vitro biological activity have a greater in vivo

efficacy due to longer half-life in the body. P. 194. However, although the reference does teach some of the conjugates, the reference does not teach the claimed G-CSF conjugates, or provide any guidance leading to the claimed conjugates.

Reidhaar-Olson et al., Biochemistry 35:9034-9041. This reference discloses a number of G-CSF substitution mutants with reduced biological activity. Among the substitutions disclosed are substitutions of Alanine for residues E19, K34, K40, and F144. Substitution of any of these residues reduced the activity of the protein to less than 25% of the wild-type protein. See, Table 1, p. 9036. Thus, the reference teaches a G-CSF mutant with between either 3-25%, or 4-20% of the wild-type activity. The reference further teaches both substitution of K16, and that that substitution of residue T105 results in a protein with higher activity than the wild-type. However, it does not teach the combining of these substitutions either with each other, or motivations to do so, or the substitution of Arginine for the residues.

Bowen et al., Exp Hematol 27: 425-32. This reference discloses that G-CSF variants with between 1-3 PEG molecules attached have longer half-lives, and therefore greater in vivo bioactivity even though the in vitro activity of these G-CSF variants is diminished. Thus, the reference teaches the G-CSF variants with between 2 and 8 polyethylene glycols. The reference also teaches that the PEG molecules have molecular weights of between 5 and 20 kDa. The reference therefore teaches variants comprising polymers with molecular weights in the ranges of 3000-12,000, 2000-20,000, and 1000-40,000 Da. However, the reference does not teach G-CSF lysine variants.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 571-272-0905. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Z. Lucas
Patent Examiner

James C. Housel 3/7/05